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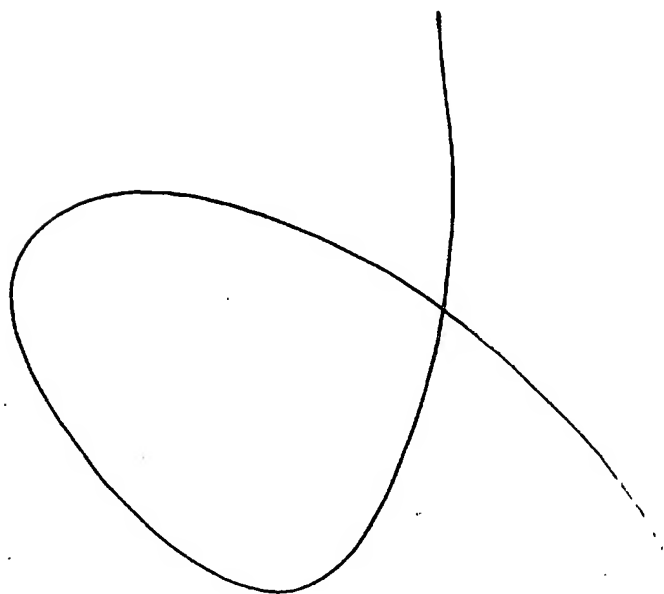
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Dated 12 July 2000



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1. Your reference

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3. Full name, address and postcode of the or of each applicant (underline all surnames)

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cf. 2/3 1/77
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SmithKline Beecham SpA
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4. Title of the invention

Novel Compounds

5. Name of your agent (if you have one)

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Country Priority application number Date of filing
(if you know it) (day / month / year)

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Request for preliminary examination and search (*Patents Form 9/77*)

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We request the grant of a patent on the basis of this application

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NOVEL COMPOUNDS

This invention relates to certain novel compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

Diseases associated with loss of bone mass are known to be caused by over activity of osteoclast cells. It is also known that certain compounds, usually related to bafilomycin, are useful for treating such diseases. For example International Application Publication Number WO 91/06296 discloses certain bafilomycin macrolides for the treatment of bone affecting diseases.

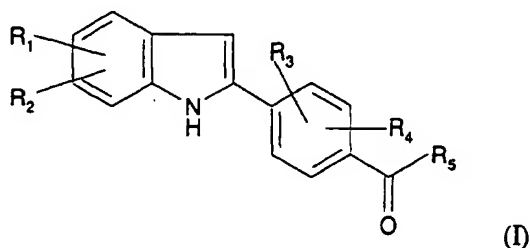
However, bafilomycin derivatives are not selective for osteoclasts in humans. The use of these compounds is therefore associated with unacceptable toxicity due to generalised blockade of other essential v-ATPases. Indeed, to date there is no known treatment which is selective for the human osteoclasts.

The search for a successful treatment for diseases associated with loss of bone mass in humans is further complicated in that the nature of the therapeutic target for the selective inhibition of the osteoclasts is controversial. Thus Baron *et al.* (International Application Publication Number WO93/01280) indicate that a specific vacuolar ATPase (V-ATPase) has been identified in osteoclasts as a potential therapeutic target. However, the Baron work was carried out in chickens and Hall *et al.* (*Bone and Mineral* 27, 159-166, (1994)), in a study relating to mammals, conclude that in contrast to avian osteoclast V-ATPase, mammalian osteoclast V-ATPase is pharmacologically similar to the v-ATPase in other cells and, therefore, it is unlikely to be a good therapeutic target.

It has now surprisingly been found that particular indole compounds are selective for mammalian osteoclasts, acting to selectively inhibit their bone resorbing activity. These compounds are therefore considered to be particularly useful for the treatment and/or prophylaxis of diseases associated with loss of bone mass, such as osteoporosis and related osteopenic diseases, Paget's disease, hyperparathyroidism and related diseases. These compounds are also considered to possess anti-tumour activity, antiviral activity (for example against *Semliki Forest*, *Vesicular Stomatitis*, *Newcastle Disease*, *Influenza A and B*, *HIV* viruses), antiulcer activity (for example the compounds may be useful for the treatment of chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), immunosuppressant activity, antilipidemic activity, antiatherosclerotic activity and to be useful for the treatment of AIDS and Alzheimer's disease. Furthermore, these compounds are also considered useful in inhibiting angiogenesis i.e. the formation of new blood vessels which is observed in various types of pathological

conditions (*angiogenic diseases*) such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours.

Accordingly, the invention provides a compound of formula (I)



or a salt thereof, or a solvate thereof, wherein;

R_1 and R_2 each independently represents methoxy or chloro;

R_3 and R_4 each independently represents hydrogen or alkoxy, and;

R_5 represents $-NR_5R_t$ wherein R_5 and R_t each independently represent hydrogen, unsubstituted or substituted alkyl, or unsubstituted or substituted heterocyclyl.

Suitable positions for substitution for R_1 or R_2 are the 4, 5, 6 or 7 position, favourably the 5 or 6 position.

In a preferred aspect R_1 is 5-chloro, and R_2 is 6-chloro.

Examples of R_3 are methoxy and ethoxy.

Suitably R_3 is located meta to the $-COR_5$ moiety.

Examples of R_4 are hydrogen and methoxy.

Suitably R_4 is located meta to the $-COR_5$ moiety.

Suitably, R_5 or R_t represent unsubstituted or substituted alkyl, or unsubstituted or substituted heterocyclyl.

When R_5 or R_t represent unsubstituted or substituted alkyl, suitable alkyl groups are C_{1-6} alkyl groups, for example C_1 , C_2 , C_3 , C_4 and C_5 alkyl groups, favourably ethyl, propyl or butyl.

When R_5 or R_t represent substituted alkyl, favoured groups are 3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl, and 3-[4-(2-pyrimidinyl)piperazin-1-yl]propyl groups.

In a favoured aspect, R_5 represents an unsubstituted or substituted piperidinyl group, especially a 4-piperidinyl group.

Substituents for the piperidinyl ring include alkyl, fused cycloalkyl, arylalkyl, hydroxyalkyl and polyhydroxyalkyl.

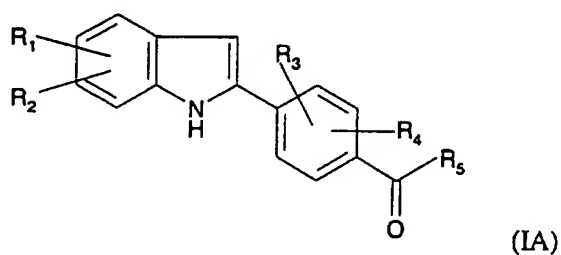
Favoured substituents for piperidinyl groups are alkyl groups.

When the piperidinyl group is substituted it is preferred that the substituents are attached to one or both of the carbon atoms alpha to the nitrogen atom.

5 Examples of substituted piperidinyl groups are 1,2,2,6,6-pentamethylpiperidin-4-yl and 2,2,6,6-tetramethylpiperidin-4-yl groups.

Favourably, R_t is hydrogen.

There is a subgroup of compounds within formula (I) of formula (IA)

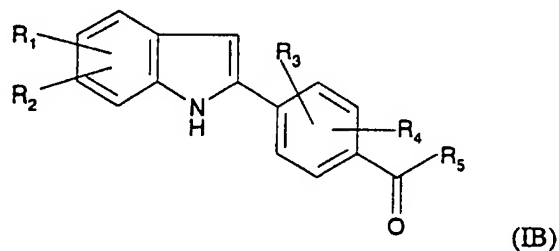


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wherein R_1 , R_2 , R_3 , R_4 , and R_5 are as defined in formula (I), R_s is 3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl or 3-[4-(2-pyrimidinyl)piperazin-1-yl]propyl, and R_t is hydrogen.

There is also a subgroup of compounds within formula (I) of formula (IB)

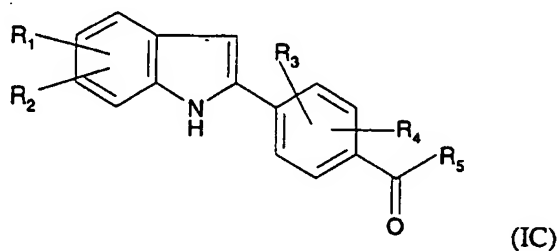
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wherein R_1 , R_2 , R_3 , R_4 , and R_5 are as defined in formula (I), R_s is 3-pyridyl or 3-(6-methoxy)pyridyl, and R_t is hydrogen.

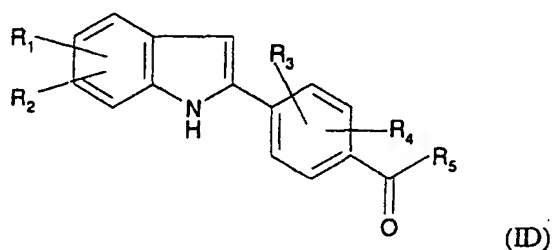
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There is also a subgroup of compounds within formula (I) of formula (IC)



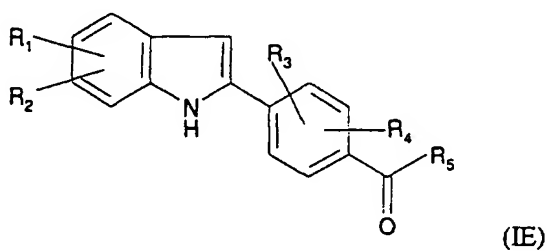
wherein R₂, R₄, and R₅ are as defined in formula (I), R_s is 2,2,6,6-tetramethylpiperidin-4-yl, R_t is hydrogen, R₃ is 3-methoxy, and R₁ is 5-chloro or 5-methoxy.

5 There is also a subgroup of compounds within formula (I) of formula (ID)



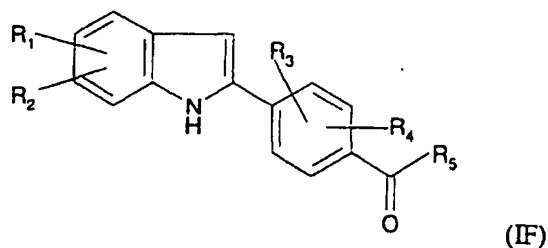
10 wherein R₁, R₂, R₄, and R₅ are as defined in formula (I), R_s is 2,2,6,6-tetramethylpiperidin-4-yl, R_t is hydrogen, and R₃ is 2-methoxy.

There is also a subgroup of compound within formula (I) of formula (IE)



15 wherein R₁, R₂, R₄, and R₅ are as defined in formula (I), R_s is 1,2,2,6,6-pentamethylpiperidin-4-yl, R_t is hydrogen, and R₃ is 2-methoxy, 3-methoxy, or 3-ethoxy.

There is also a subgroup of compounds within formula (I) of formula (IF)



20

wherein R1, R2, R3, R4, and R5 are as defined in formula (I), Rs is 1-benzylpiperidin-4-yl, and Rt is hydrogen.

As used herein, the term "alkyl" includes straight or branched chain alkyl groups having from 1 to 12, suitably 1 to 6, preferably 1 to 4, carbon atoms, such as methyl, ethyl, n- and iso-propyl and n- iso-, tert-butyl and pentyl groups, and also includes such alkyl groups when forming part of other groups such as alkoxy or alkanoyl groups.

As used herein, the term "aryl" includes phenyl and naphthyl, especially phenyl.

Suitable optional substituents for any aryl group include up to 5 substituents, suitably up to 3 substituents, selected from alkyl, alkoxy, thioalkyl, hydroxy, halo, trifluoromethyl, alkylcarbonyl, cyano, nitro, or a group -NR_uR_v wherein R_u and R_v each independently represent hydrogen, alkyl or alkylcarbonyl.

Suitable arylalkyl groups include aryl C₁₋₃alkyl groups such as phenylethyl and benzyl groups, especially benzyl.

Preferably, substituted aralkyl groups are substituted in the aryl moiety.

As used herein, the term "heterocyclyl" includes saturated or unsaturated single or fused ring heterocyclic groups, each ring having 4 to 11 ring atoms, especially 5 to 8, preferably 5, 6 or 7 which ring atoms include 1, 2 or 3 heteroatoms selected from O, S, or N.

Suitable optional substituents for any heterocyclyl group includes those mentioned herein with respect to the aryl group.

As used herein, the term "halogen" or "halo" includes fluoro, chloro, bromo and iodo, suitably fluoro and chloro, favourably chloro.

When used herein "acyl" includes alkyl carbonyl.

Certain of the carbon atoms of the compounds of formula (I) are chiral carbon atoms and may therefore provide stereoisomers of the compound of formula (I). The invention extends to all stereoisomeric forms of the compounds of formula (I) including enantiomers and mixtures thereof, including racemates.

The different stereoisomeric forms may be separated or resolved one from the other by conventional methods or any given isomer may be obtained by conventional stereospecific or asymmetric syntheses.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include acid addition salts and salts of carboxy groups.

Suitable pharmaceutically acceptable acid addition salts include salts with inorganic acids such, for example, as hydrochloric acid, hydrobromic acid, orthophosphoric acid or sulphuric acid, or with organic acids such, for example as methanesulphonic acid, toluenesulphonic acid, acetic acid, propionic acid, lactic

acid, citric acid, fumaric acid, malic acid, succinic acid, salicylic acid, maleic acid, glycerophosphoric acid or acetylsalicylic acid.

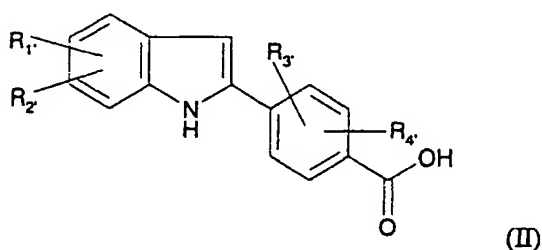
Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium and lithium, alkaline earth metal salts such as calcium or magnesium
 5 and ammonium or substituted ammonium salts, for example those with C1-6alkylamines such as triethylamine, hydroxyC1-6alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as dicyclohexylamine, or with procaine, 1,4-
 10 dibenzylpiperidine, N-benzyl-N-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

Suitable solvates of the compounds of the formula (I) are pharmaceutically acceptable solvates, such as hydrates.

15 The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form another aspect of the present invention.

20 A compound of formula (I) may be prepared by amidation of a suitable carboxylic acid with a suitable amine. Accordingly, the present invention also provides a process for the preparation of a compound of formula (I) or a salt thereof or a solvate thereof, which process comprises the amidation of a compound of formula (II)

25



wherein R₁', R₂', R₃', and R₄' each respectively represent R₁, R₂, R₃, and R₄ as defined in relation to formula (I) or a protected form thereof, with a compound of
 30 formula (III)



wherein R_5' and R_1' each represent R_5 and R_1 as defined in relation to formula (I) or a protected form thereof and thereafter, as necessary, carrying out one or more of the following steps:

(i) converting one compound of formula (I) into another compound of formula (I);

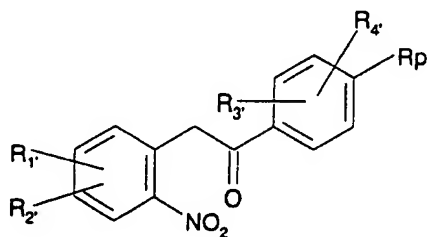
(ii) removing any protecting group;

(iii) preparing a salt or a solvate of the compound so formed.

Suitable amidation methods include treating the compound of formula (II) with a compound of formula (III).

The reaction between the compounds of formula (II) and (III) may be carried out under the appropriate conventional amidation conditions, for example in an aprotic solvent such as dimethylformamide, acetonitrile and tetrahydrofuran, at any temperature providing a suitable rate of formation of the required product, conveniently at ambient temperature; preferably the amidation reaction is carried out in the presence of a peptide coupling reagent such as 1-hydroxybenzotriazole (HOBT), and/or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC).

A compound of formula (II) may be prepared by cyclising a compound of formula (IV):



(IV)

wherein R_1 , R_2 , R_3 , and R_4 are as defined in relation to formula (II) and R_p represents a protected carboxyl group or a group convertible into a carboxyl group and thereafter, as required, converting the group R_p into a carboxyl group.

Suitably, the cyclisation reaction is carried out under reductive cyclisation conditions, for example by using powdered iron/acetic acid mixtures or an alkali metal hydrogensulphite, such as sodium hydrogensulphite, in any suitable solvent such as tetrahydrofuran, ethanol, methanol or water or mixtures thereof at any temperature providing a suitable rate of formation of the required product, such as an elevated temperature, conveniently at the reflux temperature of the solvent.

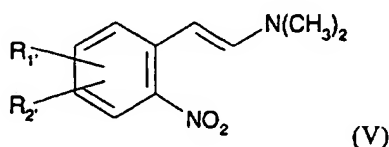
When R_p is a protecting group, suitable protecting groups include lower alkyl groups, for example methyl or ethyl groups, which may be removed by

conventional hydrolysis methods, for example by use of basic hydrolysis using ethanolic potassium hydroxide.

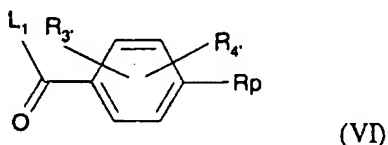
When R_p is a group convertible into a carboxyl group, suitable groups include cyano group. Such groups may be converted into carboxyl groups using conventional methods for example when R_p is a cyano group it may be converted into a carboxyl group by hydrolysis using conventional methods, for example by use of basic hydrolysis using potassium hydroxide solution in ethanol at reflux.

A preferred value of R_p is a cyano group.

A compound of formula (IV) is prepared by reacting a compound of formula (V)



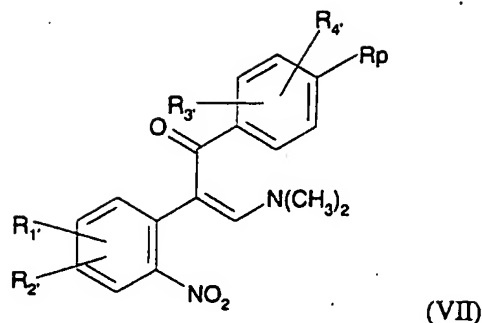
wherein R_1 and R_2 are as defined in relation to formula (II) with a compound of formula (VI)



wherein R_3 , R_4 , and R_p are as defined in relation to formula (IV) and L_1 represents a leaving group, such as a halogen group, for example a chloro group.

The reaction between the compounds of formula (V) and (VI) may be carried out in an inert hydrocarbon solvent, such as cyclohexane, at any temperature providing a suitable rate of formation of the required product, preferably at an elevated temperature, such as the reflux temperature of the solvent and in presence of a base, preferably a tertiary amine such as triethylamine.

The reaction between the compounds of formulae (V) and (VI) proceeds via an intermediate which is not usually isolated and which provides the required compound of formula (IV) on heating in situ. In an alternative aspect, the intermediate is isolated thereby providing an alternative preparation of the compound of formula (IV) wherein the compound of formula (VII)



wherein R_1 , R_2 , R_3 , and R_4 are as defined in relation to formula (II) and R_p is as defined in relation to formula (IV), is heated to provide the compound of formula (IV) as hereinbefore defined.

The conversion of compound (VII) into the compound of formula (IV) is conveniently carried out in a polar solvent mixture, such as dioxane and water, usually at the reflux temperature of the solvent mixture in conditions analogous to those described in *J. Het. Chem.* 11, 219-221, (1974).

The compounds of formula (V) are known compounds or they are prepared using methods analogous to those used to prepare known compounds, such as those disclosed by Meervein *et al Ann. Chem.* 641, 1 (1961) and *Org. Synth. Collective VII*, 34-41.

The compounds of formula (III) are known or they are prepared using methods analogous to those used to prepare known compounds, such as those described in J. March, *Advanced Organic Chemistry*, 3rd Edition (1985), Wiley Interscience.

Amines of general formula $HNRsRt'$ may be prepared using the methods known in the art for the preparation of amines, for example as taught in *Houben-Weil, Methoden der Organischen Chemie*, Vol. XI/1 (1957) and Vol. E16d/2 (1992), Georg Thieme Verlag, Stuttgart.

A compound of formula (I) or a salt thereof or a solvate thereof may be isolated from the above mentioned processes according to standard chemical procedures.

The preparation of salts and/or solvates of the compounds of formula (I) may be performed using the appropriate conventional procedure.

If required mixtures of isomers of the compounds of the invention may be separated into individual stereoisomers and diastereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent. Suitable optically active acids which may be used as resolving agents are described in "*Topics in Stereochemistry*", Vol. 6, Wiley Interscience, 1971, Allinger, N.L. and Eliel, W.L. Eds.

Alternatively, any enantiomer of a compound of the invention may be obtained by stereospecific synthesis using optically pure starting materials of known configuration.

5 The absolute configuration of compounds may be determined by conventional methods such as X-ray crystallographic techniques.

The protection of any reactive group may be carried out at any appropriate stage in the aforementioned processes. Suitable protecting groups include those used conventionally in the art for the particular group being protected. Protecting groups may be prepared and removed using the appropriate conventional
10 procedure, for example OH groups, including diols, may be protected as the silylated derivatives by treatment with an appropriate silylating agent such as di-tert-butylsilylbis(trifluoromethanesulfonate). The silyl group may then be removed using conventional procedures such as treatment with hydrogen fluoride, preferably in the form of a pyridine complex and optionally in the presence of
15 alumina, or by treatment with acetyl chloride in methanol. Alternatively benzyloxy groups may be used to protect phenolic groups, the benzyloxy group may be removed using catalytic hydrogenolysis using such catalysts as palladium (II) chloride or 10% palladium on carbon.

Amino groups may be protected using any conventional protecting group,
20 for example tert-butyl esters of carbamic acid may be formed by treating the amino group with di-tert-butyl dicarbonate, the amino group being regenerated by hydrolysing the ester under acidic conditions, using for example hydrogen chloride in aqueous ethanol or trifluoroacetic acid in methylene dichloride. An amino group may be protected as a benzyl derivative, prepared from the appropriate
25 amine and a benzyl halide under basic conditions, the benzyl group being removed by catalytic hydrogenolysis, using for example a palladium on carbon catalyst.

Indole NH groups and the like may be protected using any conventional group, for example benzenesulphonyl, methylsulphonyl, tosyl, formyl, acetyl (all of them removable by treatment with alkaline reagents), benzyl (removable either
30 with sodium in liquid ammonia or with $AlCl_3$ in toluene), allyl (removable by treatment with rhodium (III) chloride under acidic conditions), benzyloxycarbonyl (removable either by catalytic hydrogenation or by alkaline treatment), trifluoroacetyl (removable by either alkaline or acidic treatment), t-butyl dimethylsilyl (removable by treatment with tetrabutylammonium fluoride), 2-
35 (trimethylsilyl)ethoxymethyl (SEM) (removable by treatment with tetrabutylammonium fluoride in the presence of ethylenediamine), methoxymethyl (MOM) or methoxyethyl (MEM) groups (removed by mild acidic treatment).

Carboxyl groups may be protected as alkyl esters, for example methyl esters, which esters may be prepared and removed using conventional procedures,

one convenient method for converting carbomethoxy to carboxyl is to use aqueous lithium hydroxide.

A leaving group is any group that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site.

- 5 Suitable examples of such groups unless otherwise specified are halogen groups, mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

The salts, esters, amides and solvates of the compounds mentioned herein may as required be produced by methods conventional in the art. For example, acid addition salts may be prepared by treating a compound of formula (I) with the
10 appropriate acid.

Esters of carboxylic acids may be prepared by conventional esterification procedures, for example alkyl esters may be prepared by treating the required carboxylic acid with the appropriate alkanol, generally under acidic conditions.

Amides may be prepared using conventional amidation procedures, for
15 example amides of formula CONR_5R_1 may be prepared by treating the relevant carboxylic acid with an amine of formula HNR_5R_1 , wherein R_5 and R_1 are as defined above. Alternatively, a C_{1-6} alkyl ester such as a methyl ester of the acid may be treated with an amine of the above defined formula HNR_5R_1 to provide the required amide, optionally in presence of trimethylaluminium following the
20 procedure described in *Tetrahedron Lett.* 48, 4171-4173, (1977).

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties.

The present invention therefore provides a method for the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals
25 which method comprises the administration of an effective non-toxic amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof.

In a further aspect, the present invention provides a method for the treatment of osteoporosis and related osteopenic diseases in a human or
30 non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.

In a further aspect, the present invention also provides a method for the
35 treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia, viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), autoimmune diseases and transplantation, for the treatment

and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours, in a human or non-human mammal. which comprises administering an effective, non-toxic, amount of a compound of
 5 formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.

In a still further aspect, the present invention a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

10 In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for use in the treatment or prophylaxis of diseases associated with over activity of osteoclasts in mammals.

In a further aspect, the present invention provides a compound of formula
 15 (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, for use in the treatment of or prophylaxis of osteoporosis and related osteopenic diseases.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for use in the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia, viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), autoimmune diseases and transplantation,
 20 for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours, in a human or non-human mammal.

Of particular interest is the osteoporosis associated with the peri and post
 30 menopausal conditions. Also encompassed are the treatment and prophylaxis of Paget's disease, hypercalcemia associated with bone neoplasms and all the types of osteoporotic diseases as classified below according to their etiology:

Primary osteoporosis

35 **Involutional**

Type I or postmenopausal

Type II or senile

Juvenile

Idiopathic in young adults

Secondary osteoporosis

- Endocrine abnormality
- Hyperthyroidism
- 5 Hypogonadism
 - Ovarian agenesis or Turner's syndrome
 - Hyperadrenocorticism or Cushing's syndrome
 - Hyperparathyroidism
 - Bone marrow abnormalities
- 10 Multiple myeloma and related disorders
 - Systemic mastocytosis
 - Disseminated carcinoma
 - Gaucher's disease
 - Connective tissue abnormalities
- 15 Osteogenesis imperfecta
 - Homocystinuria
 - Ehlers-Danlos syndrome
 - Marfan's syndrome
 - Menke's syndrome
- 20 Miscellaneous causes
 - Immobilisation or weightlessness
 - Sudeck's atrophy
 - Chronic obstructive pulmonary disease
 - Chronic alcoholism
- 25 Chronic heparin administration
 - Chronic ingestion of anticonvulsant drugs

- In addition the invention encompasses the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia,
- 30 viral conditions (for example those involving *Semliki Forest* virus, *Vesicular Stomatitis* virus, *Newcastle Disease* virus, *Influenza A* and *B* viruses, *HIV* virus), ulcers (for example chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), for use as immunosuppressant agents in autoimmune diseases and transplantation, antilipidemic agents for the treatment and/or prevention of
 - 35 hypercholesterolemic and atherosclerotic diseases and to be useful for the treatment of AIDS and Alzheimer's disease. These compounds are also considered useful in treating angiogenic diseases, i.e. those pathological conditions which are dependent on angiogenesis, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours.

A compound of formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

5 Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof and a pharmaceutically acceptable carrier therefor.

10 Active compounds or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof are normally administered in unit dosage form.

15 An amount effective to treat the disorders hereinbefore described depends upon such factors as the efficacy of the active compounds, the particular nature of the pharmaceutically acceptable salt or pharmaceutically acceptable solvate chosen, the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 0.01 to 50 mg, for example 1 to 25 mg, of the compound of the invention. Unit doses will normally be administered once or more than once a day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 3 or 2 to 4 times a day such that the total daily dose is normally in the range, for a 70 kg adult of 0.01 to 250 mg, more usually 1 to 100 mg, for example 5 to 70 mg, that is in the range of approximately 0.0001 to 3.5 mg/kg/day, more usually 0.01 to 1.5 mg/kg/day, for example 0.05 to 0.7 mg/kg/day.

25 In such treatments the active compound may be administered by any suitable route, e.g. by the oral, parenteral or topical routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a human or veterinary pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

30 Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusible solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient
35 for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents,

tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

For topical administration, the composition may be in the form of a transdermal ointment or patch for systemic delivery of the active compound and

may be prepared in a conventional manner, for example, as described in the standard textbooks such as 'Dermatological Formulations' - B.W. Barry (Drugs and the Pharmaceutical Sciences - Dekker) or Harrys Cosmeticology (Leonard Hill Books).

5 Accordingly, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals.

10 In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of osteoporosis and related osteopenic diseases.

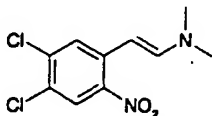
15 In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia., viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), autoimmune diseases and transplantation, for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours,.

20 No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention. As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

25 The following, descriptions, examples and pharmacological methods illustrate the invention but do not limit it in any way.

Descriptions and Examples

Description 1: *trans*-4,5-Dichloro-2-nitro- β -dimethylaminostyrene

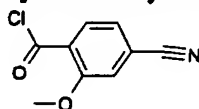


35

A solution of 10.3 g (50 mmol) of 4,5-dichloro-2-nitrotoluene (*Helv. Chim. Acta* 1936, 19, 434-439) in a mixture of 11.9 g (100 mmol) *N,N*-dimethylformamide

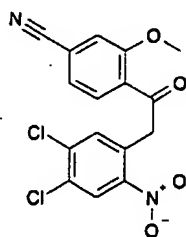
dimethylacetal in DMF (25 ml) was heated at 100°C for 16 h. The dark reaction mixture was concentrated *in vacuo*, the residue diluted with methylene chloride and washed twice with water. The organic solution was dried over MgSO_4 , concentrated *in vacuo* affording 12.6 g (48 mmol, yield 96.5%) of the title compound as dark red crude crystals.

Description 2: 2-Methoxy-4-cyanobenzoyl chloride



2-Methoxy-4-cyanobenzoic acid (*Tetrahedron Letters*, 1986, 27(49), 5997-6000) (1 g, 5.6 mmol) was dissolved in CH_2Cl_2 (20 ml). Oxalyl chloride (1.5 ml, 8.2 mmol) was rapidly introduced into the solution and a drop of DMF was added. A vigorous reaction took place with the abundant evolution of gaseous products. The solution was stirred for 1 h then allowed to stand over night. Solvent was removed using a rotary evaporator to leave 1.1 g of an off white solid (5.6 mmol, yield 99%) that was used without further purification.

Description 3: 3-Methoxy-4-[2-[(4,5-dichloro-2-nitro)phenyl]-1-oxo-ethyl]-benzonitrile

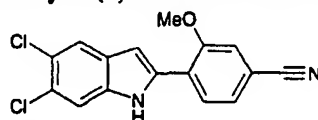


2-Methoxy-4-cyanobenzoyl chloride (1.1 g, 5.6 mmol), prepared as in Description 3, was added portionwise to a stirred solution of *trans*-4,5-dichloro-2-nitro- β -dimethylaminostyrene (1.47 g, 5.6 mmol) and triethylamine (1.5 ml, 10 mmol) in cyclohexane (20 ml). The solution was then refluxed for 16 h. The reaction was cooled and all the volatile products removed using a rotary evaporator. A dark residue was obtained which was then dissolved in CH_2Cl_2 (40 ml) and washed once with 10% Na_2CO_3 solution (20 ml). The organic layer was then dried with anhydrous Na_2SO_4 , filtered and the solvent removed using a rotary evaporator. Dark brown to black powder (2.42 g) was obtained that was dissolved in as little ethyl acetate as possible and hexane was added to this solution to precipitate light brown powder (1.72 g, mp= 167-170°C) that was used without further purification in the next step.

This crude intermediate (1.2 g) was dissolved in 1,4-dioxane (20 ml) and water (10 ml) was added. The solution was refluxed for 48 h, filtered while still hot and then chilled in an ice water bath. Yellow to brown crystals were collected on a Buchner funnel obtaining 0.60 g (1.6 mmol, yield 30%) of the title compound, mp = 171-174 °C.

¹H NMR (CDCl₃) δ = 8.27 (s, 1H); 7.81 (d, 1H); 7.49 (s, 1H); 7.35 (dd, 1H); 7.28 (d, 1H); 4.61 (s, 2H); 4.00 (s, 3H).

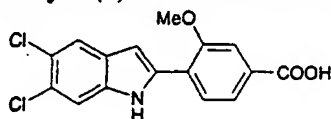
Description 4: 3-Methoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzonitrile



3-Methoxy-4-[2-(4,5-dichloro-2-nitro)phenyl-1-oxo-ethyl]-benzonitrile (0.4 g, 1.0 mmol) was dissolved in EtOH (10 ml) and AcOH (10 ml). The solution was brought to gently reflux and iron powder (0.5 g, 9 mmol) was added in small portions over the period of an hour. The solution was refluxed for 12 h after which the solvents were removed using a rotary evaporator. The residue was extracted several times with THF. After removal of the solvent, crude 3-methoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzonitrile (0.35 g, 1.0 mmol, yield 100%) was obtained that was used in the next step without further purification. mp = 241-244 °C.

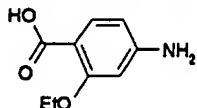
¹H NMR (DMSO-*d*₆) δ = 11.60 (s br, 1H); 7.98 (d, 1H); 7.85 (s, 1H); 7.67 (s, 1H); 7.65 (d, 1H); 7.55 (dd, 1H); 7.14 (s, 1H); 4.00 (s, 3H).

Description 5: 3-Methoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzoic acid



3-Methoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzonitrile (0.35 g, 1.0 mmol) was suspended in 30 % NaOH (20 ml) and 95% EtOH (20 ml). The mixture was refluxed for 12 h and then allowed to cool to room temperature. The suspension was concentrated to about half volume using a rotary evaporator and then filtered on a Buchner funnel obtaining a tan to yellow coloured powder. This was stirred for 2 hour in 10% HCl. The solution was then filter to yield 0.256 g (0.76 mmol, yield 69%) of the crude title compound that was purified by chromatography to yield 150 mg of pure title compound, mp > 270 °C.

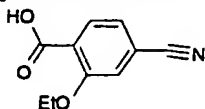
¹H NMR (DMSO-*d*₆) δ = 11.60 (broad s, 1H); 7.92 (d, 1H); 7.83 (s, 1H); 7.66 (m, 3H); 7.10 (s, 1H); 4.02 (s, 3H).

Description 6: 2-Ethoxy-4-aminobenzoic acid

A suspension of methyl 2-ethoxy-4-acetamidobenzoate (50 g, 211 mmol) in aqueous solution of NaOH (15% W/W, 200 ml) was gently refluxed for 16 hours.

- 5 The resulting pale brown solution was allowed to cool to room temperature and then further cooled in an ice water bath. Concentrated HCl (37% w/w) was added until the solution reached a pH of 6. The solid precipitated from the solution was filtered under vacuum, dried at 50°C to give 38.3 g of the title compound (yield 100%).

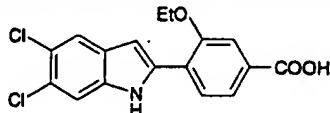
10

Description 7: 2-Ethoxy-4-cyanobenzoic acid

- In a 1l reactor equipped with a sealed mechanical stirrer, CuCN (12 g, 134 mmol) were suspended in 100 ml of distilled water. NaCN (18.3 g, 373 mmol) was added with vigorous stirring and the internal temperature was kept below 40°C until all the CuCN went into solution. The suspension of 2-ethoxy-4-aminobenzoic acid (20 g, 110 mmol) in water (200 ml) and concentrated HCl (33 ml) was stirred and cooled in an ice bath. When the temperature reached 5°C, a solution of NaNO₂ (9.7 g, 140 mmol) in water (30 ml) was added dropwise at such a rate as to maintain the temperature below 5 °C.

- 20 When all the NaNO₂ was added, the solution was slowly introduced through an ice cooled dropped funnel into the reactor containing the NaCN/CuCN solution. A reaction took place with the vigorous formation of N₂. A few drops of octanol were added to keep the foaming under control. Stirring was continued for 4 h. The resulting suspension was then extracted with ethyl acetate (3x100 ml) and the organic phase dried over MgSO₄ and evaporated under vacuum obtaining 15 g of the title compound (yield 71.1 %) as a light brown powder, mp = 170-172°C.

25

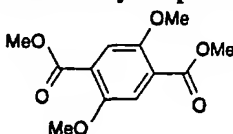
Description 8: 3-Ethoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzoic acid

30

The title compound was prepared starting from 2-ethoxy-4-cyanobenzoic acid. prepared as in Description 7, following the procedure in Description 1-5. The title

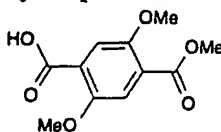
compound was prepared with an overall yield of 18 %, based on the 2-ethoxy-4-cyanobenzoic acid.

Description 9: Dimethyl 2,5-dimethoxyterephthalate



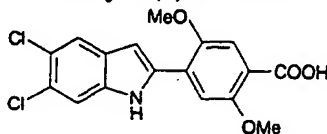
5 A suspension of 2,5-dihydroxyterephthalic acid (5 g, 25 mmol), K₂CO₃ (10 g, 72 mmol) and dimethyl sulphate (11 ml, 116 mmol) in acetone (100 ml) was stirred and refluxed for 24. The mixture was filtered while still hot and the solvent was evaporated to about half of the original volume. On cooling white needles
10 precipitated and were filtered and dried obtaining 4.6 g of the title compound (yield 73%), mp = 141-143°C.

Description 10: 2,5-Dimethoxyterephthalic acid monomethyl ester



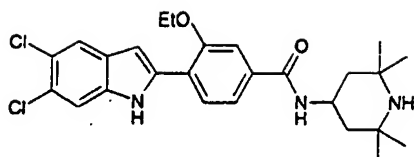
15 A suspension of dimethyl 2,5-dimethoxyterephthalate (4 g, 15.7 mmol), prepared as in Description 9, in methanolic KOH (0.86 g of KOH in 100 ml MeOH) was refluxed for 3 h. The solution was cooled and the solvent removed under vacuum. The residue was treated with dilute HCl and the solid filtered off. The crude mixture was purified by column chromatography using 1:1 ethyl acetate/hexane as
20 a solvent obtaining 1.72 g of the title compound (yield 44.7%), mp = 123-124°C

Description 11: 2,5-Dimethoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzoic acid



25 The title compound was prepared starting from 2,5-dimethoxyterephthalic acid monomethyl ester, prepared as in Description 10, following the procedure in Description 1-5. The title compound was prepared with an overall yield of 46%, based on 2,5-dimethoxyterephthalic acid monomethyl ester

30 **Example 1: 4-(5,6-Dichloro-1H-indol-2-yl)-3-ethoxy-N-(2,2,6,6-tetramethylpiperidin-4-yl)-benzamide**



To a suspension of 3-ethoxy-4-(5,6-dichloro-1H-indol-2-yl)-benzoic acid (200 mg, 0.57 mmol), prepared as in Description 8, in CH₃CN (14 ml) and THF (6 ml), WSC (N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) (104 mg, 55 mmol) and 1-hydroxybenzotriazole (77 mg, 0.57 mmol) were added and the reaction was refluxed for 3h.

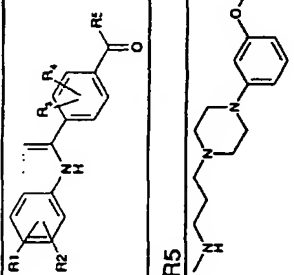
4-Amino-2,2,6,6-tetramethylpiperidine (108 mg, 0.7 mmol) were introduced into the reaction mixture and refluxing continued for another 2h. The reaction was cooled and the solvent was removed under vacuum. The residue was treated with 30 ml of 10% NaOH solution and then filtered. The resulting solid was washed with water, dried and purified by chromatography on silica gel to yield 154 mg of the title compound as light yellow powder (yield 55%), mp = 253-255 °C.

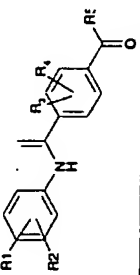
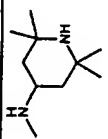
¹H NMR (DMSO-*d*₆) δ = 11.56 (s br, 1H); 8.28 (d br, 1H); 7.85 (d, 1H); 7.82 (s, 1H) 7.64 (s, 1H); 7.59 (s, 1H); 7.57 (d, 1H); 7.11 (s, 1H); 4.40-4.21 (m, 1H); 4.30 (q, 2H); 1.80 (d br, 2H); 1.50 (t, 3H); 1.30 (m, 2H); 1.28 (s, 6H); 1.15 (s, 6H).

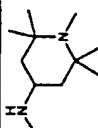

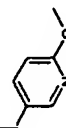
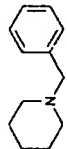
ESI POS; AQA ; solvent: MeOH / spray 3 kV / skimmer: 20 V/ probe 135°C: m/z 488 (MH⁺)

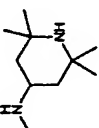
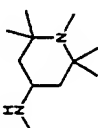
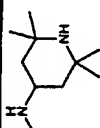
The Example compounds listed in Table 1 were prepared according to the procedure of Example 1:

Table 1

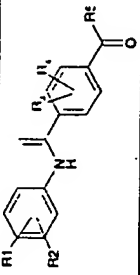
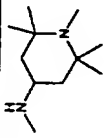
Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
2	4-(5,6-Dichloro-1H-indol-2-yl)-N-[3-(4-(3-methoxyphenyl)pyrazin-1-yl)propyl]-3-methoxybenzamide	5-Cl	6-Cl	3-OMe	-H		A) ESI POS; TSQ 700; solvent: MeOH / spray 4.5 kV / skimmer: 60 V; capillary 220°C : m/z 474 (MH ⁺) B) CID Offset = -56 V : m/z 567; 375; 318.	201-205	¹ H-NMR (DMSO-d ₆) δ = 11.53 (s br, 1H); 8.55 (t br, 1H); 7.88 (d, 1H); 7.81 (s, 1H); 7.66 (s, 1H); 7.60 (d, 1H); 7.57 (dd, 1H); 7.10 (dd, 1H); 7.04 (m, 1H); 6.51 (dd, 1H); 6.43 (dd, 1H); 6.35 (dd, 1H); 4.00 (s, 3H); 3.70 (s, 3H); 3.30 (m, 2H); 3.13 (m, 4H); 2.58 (m, 4H); 2.41 (t, 2H); 1.80-1.72 (m, 2H).

Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
3	4-(5,6-Dichloro-1H-indol-2-yl)-N-[3-[4-(2-pyrimidinyl)piperazin-1-yl]propyl]-3-methoxybenzamide	5-Cl	6-Cl	3-OMe	-H		A) ESI POS; TSQ 700; solvent: MeOH / spray 4.5 kV / skimmer: 60 V / capillary 220°C : m/z 539 (MH ⁺) B) CID Offset = -56 V : m/z 539; 575; 318.	234-237	¹ H-NMR (DMSO-d ₆ at 343 K) δ = 11.30 (s br, 1H); 8.32 (d, 2H); 8.31 (t br, 1H); 7.85 (d, 1H); 7.79 (s, 1H); 7.68 (s, 1H); 7.60 s br, 1H); 7.56 (d, 1H); 7.01 (s br, 1H); 6.59 (t, 1H); 4.02 (s, 3H); 3.77 (m, 4H); 3.40 (dt, 2H); 2.50-2.40 (m, 6H); 1.87-1.73 (m, 2H).
4	4-(5,6-Dichloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-3-methoxybenzamide	5-Cl	6-Cl	3-OMe	-H		A) ESI POS; TSQ 700; solvent: MeOH / spray 4.5 kV / skimmer: 60 V / capillary 220°C : m/z 474 (MH ⁺) B) CID Offset = -56 V : m/z 474; 457; 401; 318; 290; 123; 58.	151-156	¹ H-NMR (DMSO-d ₆) δ = 11.30 (s br, 1H); 7.95 (d br, 1H); 7.82 (d, 1H); 7.77 (s, 1H); 7.68 (s, 1H); 7.61 (d, 1H); 7.56 (dd, 1H); 7.01 (d, 1H); 4.45-4.30 (m, 1H); 4.01 (s, 3H); 1.80 (m, 2H); 1.30 (m, 2H); 1.30 (s, 6H); 1.15 (s, 6H).

Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
5	4-(5,6-Dichloro-1H-indol-2-yl)- N-(1,2,2,6,6- pentamethylpiperidin-4-yl)-3- ethoxybenzamide	5-Cl	6-Cl	3-OEt	-H		ESI POS; AQA; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C; m/z 502 (MH ⁺)	> 250	¹ H-NMR (DMSO-d ₆) δ = 11.5 (s br, 1H); 8.22 (d br, 1H); 7.85 (d, 1H); 7.82 (s, 1H); 7.63 (s, 1H); 7.58 (s, 1H); 7.57 (d, 1H); 7.10 (s br, 1H); 4.29 (q, 2H); 4.29-4.14 (m, 1H); 2.22 (s, 3H); 1.75 (dd, 2H); 1.50 (t, 2H); 1.49 (t, 3H); 1.12 (s, 6H); 1.08 (s, 6H).
6	4-(5,6-Dichloro-1H-indol-2-yl)- N-(3-pyridyl)-3- ethoxybenzamide	5-Cl	6-Cl	3-OEt	-H			237-239	
7	4-(5,6-Dichloro-1H-indol-2-yl)- N-(3-(6-methoxypyridyl))-3- ethoxybenzamide	5-Cl	6-Cl	3-OEt	-H			258-260	
8	4-(5,6-Dichloro-1H-indol-2-yl)- N-(1-benzylpiperidin-4-yl)-3- ethoxybenzamide hydrochloride	5-Cl	6-Cl	3-OEt	-H			295	

Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
9	4-(5,6-Dichloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-2,5-dimethoxybenzamide	5-Cl	6-Cl	2-OMe	5-OMe		A) EI; TSQ 700; 400 mA; 70 V; m/z 567 (MH ⁺) B) ESI POS; AQA; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C; m/z 504 (MH ⁺)	148-152	¹ H-NMR (DMSO-d ₆) δ = 11.60 (s br, 1H); 7.95 (d br, 1H); 7.82 (s, 1H); 7.69 (s, 1H); 7.52 (s, 2H); 7.13 (s br, 1H); 4.40-4.21 (m, 1H); 4.00 (s, 3H); 3.92 (s, 3H); 1.78 (dd, 2H); 1.20 (s, 6H); 1.12 (dd, 2H); 1.06 (s, 6H).
10	4-(5,6-Dichloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-2,5-dimethoxybenzamide	5-Cl	6-Cl	2-OMe	5-OMe		A) ESI POS; TSQ 700; solvent: MeOH / spray 4.5 kV / skimmer: 60 V/ capillary 220°C; m/z 518 (MH ⁺) B) ESI DAU +518 (Collision gas: Argon); m/z 518; 487; 431; 365; 348; 123.	143-147	¹ H-NMR (DMSO-d ₆) δ = 11.58 (s br, 1H); 7.95 (d br, 1H); 7.81 (s, 1H); 7.68 (s, 1H); 7.51 (s, 2H); 7.13 (s br, 1H); 4.28-4.10 (m, 1H); 3.95 (s, 3H); 3.90 (s, 3H); 2.20 (s, 3H); 1.78 (dd, 2H); 1.39 (dd, 2H); 1.10 (s, 6H); 1.06 (s, 6H).
11	4-(5-Methoxy-6-chloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-3-methoxybenzamide	5-OMe	6-Cl	3-OMe	-H				

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Ex.	Name	R1	R2	R3	R4	R5	MS	MP °C	N.M.R.
12	4-(5-Methoxy-6-chloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-3-methoxybenzamide	5-OMe	6-Cl	3-OMe	-H				

Biological Assays

Background. It is known that, upon attachment to bone, an electrogenic H^+ - adenosine triphosphatase (ATPase) is polarised to the osteoclast-bone interface. The pump transports massive quantities of protons into the resorption microenvironment to effect mobilisation of the bone mineral and to create the acidic pH required by collagenases to degrade the bone matrix.

The vacuolar nature of the osteoclast proton pump was originally recognised by Blair [H. C. Blair et al., *Science*, **245**, 855 (1989)] and then confirmed by Bekker [P.J. Bekker et al., *J. Bone Min. Res.*, **5**, 569 (1990)] and Väänänen [H.K. Väänänen et al., *J. Cell. Biol.*, **111**, 1305 (1990)]. Evidence was based upon preparations of ruffled membrane fragments from avian osteoclasts (obtained from the medullar bone of calcium-starved egg-laying hens). The resulting membrane vesicles acidify in response to ATP, which is easily assessed by measuring the fluorescence quench of acridine orange, a weak base which accumulates into acidic compartments.

The biochemical pattern indicated that the osteoclast proton pump belonged to the vacuolar-like ATPases since proton transport was inhibited by N-ethylmaleimide (NEM), a sulphhydryl reagent, and by bafilomycin A_1 , a selective inhibitor of vacuolar H^+ -ATPases [J.E. Bowman et al., *Proc. Natl. Acad. Sci. USA*, **85**, 7972 (1988)], whilst it was not inhibited by ouabain, an inhibitor of Na^+/K^+ -ATPases; sodium orthovanadate, an inhibitor of P-ATPases, or by omeprazole or SCH 28080, both of which are inhibitors of gastric H^+/K^+ -ATPase [J.P. Mattsson et al., *Acta Physiol. Scand.*, **146**, 253 (1992)].

It is known that specific inhibitors of vacuolar ATPases, such as bafilomycin A_1 , are able to inhibit bone resorption in osteoclast cultures [K. Sundquist et al., *Biochem. Biophys. Res. Commun.* **168**, 309-313 (1990)]

Inhibition of Proton Transport and v-ATPase Activity in Membrane Vesicles.

Preparation of crude bone microsomes from calcium-starved egg-laying hens. Vesicles were prepared from medullar bone obtained from tibiae and femurs of egg-laying hens which were calcium-starved for at least 15 days. Briefly, bone fragments were scraped with a 24 scalpel blade, suspended in 40 ml of isolation medium (0.2 M sucrose, 50 mM KCl, 10 mM Hepes, 1 mM EGTA, 2 mM dithiothreitol, pH 7.4) and filtered through a 100 μ m pore size nylon mesh. The whole procedure was performed at 4°C. After homogenisation in a potter (20 strokes) in 40 ml of isolation medium an initial centrifugation ($6,500 \times g_{max}$ x 20 min) was performed to remove mitochondria and lysosomes. The supernatant was centrifuged at $100,000 \times g_{max}$ for 1 hr and the pellet was collected in 1 ml of isolation medium, divided into 200 μ l

aliquots, immediately frozen in liquid nitrogen and stored at -80°C . The protein content was determined using a Biorad colourimetric kit according to Bradford [M. Bradford, *Anal. Biochem.*, **72**, 248 (1976)]. For the proton transport assay, 5-10 μl of membranes were used.

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Purification of osteoclast membranes. 1 ml of crude microsomal vesicles prepared above were applied (about 0.2 ml per tube) on the top of a sucrose step-gradient consisting of 3.5 ml of 15%, 30% and 45 % (w/w) sucrose in isolation medium and centrifuged at $280,000 g_{\text{max}}$ for 2 h (SW 41 Ti rotor). After centrifugation the 30-45% sucrose interfaces were collected, diluted approx. 20-fold in isolation medium and pelleted at $100,000 g_{\text{max}}$ for 1 hour (SW 28 rotor). The pellet was then resuspended in 1 ml of isolation medium, aliquoted and frozen in liquid N_2 and stored at -80°C until used.

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Human kidney membranes were obtained from the cortex of a human kidney, frozen immediately after surgery, according to the method reported in the literature for bovine kidney (S. Gluck, *J. Biol. Chem.*, **265**, 21957 (1990)).

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Preparation of human osteoclast microsomal vesicles. Osteoclast-like giant cells isolated from osteoclastoma tumor were homogenized with a glass-teflon homogenizer (1000 rpm x 20 strokes), and the material was centrifuged at $6000 \times g_{\text{max}}$ for 20 minutes. The resulting pellet was then spun at $100,000 \times g_{\text{max}}$ for 60 minutes to pellet the microsomal fraction. Resuspended in 1 ml of isolation medium pH 7.4, frozen by liquid nitrogen immersion and stored at -80°C until used.

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Proton transport in membrane vesicles was assessed, semi-quantitatively, by measuring the initial slope of fluorescence quench of acridine orange (excitation 490 nm; emission 530 nm) after addition of 5-20 μl of membrane vesicles in 1 ml of buffer containing 0.2 M sucrose, 50 mM KCl, 10 mM Hepes pH 7.4, 1 mM ATP.Na_2 , 1 mM CDTA, 5 μM valinomycin and 4 μM acridine orange. The reaction was started by addition of 5 mM MgSO_4 . Results were expressed as the percent of the mean of two controls.

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Inhibition of bafilomycin-sensitive ATPase activity was assessed in purified membrane vesicles by measuring the release of inorganic phosphate (Pi) during 30 min of incubation at 37°C in a 96-well plate either in the presence or in the absence of bafilomycin A1. The reaction medium contained 1 mM ATP, 10 mM HEPES-Tris pH 8, 50 mM KCl, 5 μM valinomycin, 5 μM nigericin, 1 mM CDTA-Tris, 100 μM ammonium molybdate, 0.2 M sucrose and membranes (20 μg protein/ml). The reaction was initiated by MgSO_4 (8-arm pipette) and stopped, after 30 min, by addition of 4 volumes of the malachite green reagent (96-arm pipette) prepared according to Chan [*Anal. Biochem.* **157**, 375 (1986)]. Absorbance at 650 nm was

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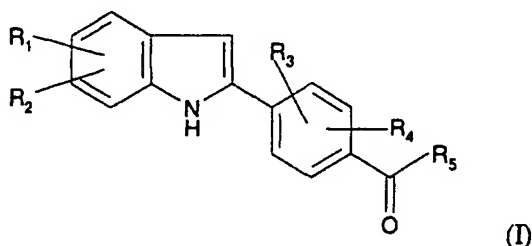
measured after 2 min using a microplate reader. Results are expressed as $\text{nmol (Pi)} \times \text{mg protein}^{-1} \times \text{min}^{-1}$ and, for each experiment, represent the mean \pm sem of triplicates.

Pharmacological Data

- 5 Compounds described in the present invention are able to inhibit bafilomycin-sensitive ATPase of chicken osteoclast in a range from 50 nM to 2 μM and of human osteoclast in a range from 30 nM to 5 μM .

Claims:

1. A compound of formula (I)



or a salt thereof, or a solvate thereof, wherein;

R_1 and R_2 each independently represents methoxy or chloro;

R_3 and R_4 each independently represents hydrogen or alkoxy, and;

- 10 R_5 represents $-NR_S R_t$ wherein R_S and R_t each independently represent hydrogen, unsubstituted or substituted alkyl, or unsubstituted or substituted heterocyclyl.

- 15 2. A compound according to claim 1 wherein R_1 and R_2 each independently represents chloro.

3. A compound according to claim 2 wherein R_1 is 5-chloro and R_2 is 6-chloro.

- 20 4. A compound according to any one claims 1 to 3 wherein R_S or R_t represents unsubstituted or substituted alkyl or unsubstituted or substituted heterocyclyl.

- 25 5. A compound according to claim 4 wherein R_S or R_t represent unsubstituted or substituted C_{1-6} alkyl groups.

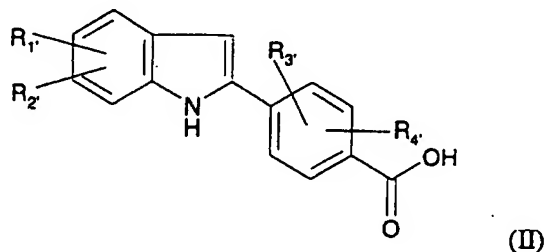
6. A compound according to claim 4 wherein R_S or R_t represent 3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl or 3-[4-(2-pyrimidinyl)piperazin-1-yl]propyl groups.

- 30 7. A compound according to claim 4 wherein R_S represents an optionally substituted piperidinyl group.

8. A compound according to claim 7 wherein R₅ represents a 1,2,2,6,6-pentamethylpiperidin-4-yl group or a 2,2,6,6-tetramethylpiperidin-4-yl group.
9. A compound according to any one of claims 1 to 8 wherein R₁ is hydrogen.
10. A compound according to any one of claims 1 to 9 wherein R₃ is methoxy or ethoxy.
11. A compound according to claim 10 wherein R₃ is located meta to the -COR₅ moiety.
12. A compound according to any one of claims 1 to 11 wherein R₄ is hydrogen or methoxy.
13. A compound according to claim 12 wherein the R₄ group is located meta to the -COR₅ moiety.
14. A compound according to any one of claims 1 to 13 selected from
 - 4-(5,6-dichloro-1H-indol-2-yl)-N-[3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl]-3-methoxybenzamide;
 - 4-(5,6-dichloro-1H-indol-2-yl)-N-[3-[4-(2-pyrimidyl)piperazin-1-yl]propyl]-3-methoxybenzamide;
 - 4-(5,6-dichloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-3-methoxybenzamide;
 - 4-(5,6-dichloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-3-methoxybenzamide;
 - 4-(5,6-dichloro-1H-indol-2-yl)-N-(3-pyridyl)-3-ethoxybenzamide;
 - 4-(5,6-dichloro-1H-indol-2-yl)-N-(3-(6-methoxypyridyl))-3-ethoxybenzamide;
 - 4-(5,6-dichloro-1H-indol-2-yl)-N-(1-benzylpiperidin-4-yl)-3-ethoxybenzamide;
 - 4-(5,6-dichloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-2,5-dimethoxybenzamide;
 - 4-(5,6-dichloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-2,5-dimethoxybenzamide;
 - 4-(5-methoxy-6-chloro-1H-indol-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-3-methoxybenzamide, and;
 - 4-(5-methoxy-6-chloro-1H-indol-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-3-methoxybenzamide;
 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof.

15. A process for the preparation of a compound of formula (I) or a salt thereof or a solvate thereof, which process comprises the amidation of a compound of formula (II)

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wherein R_1 , R_2 , R_3 , and R_4 each respectively represent R_1 , R_2 , R_3 , and R_4 as defined in relation to formula (I) or a protected form thereof, with a compound of formula (III)

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wherein R_5 and R_t each represent R_5 and R_t as defined in relation to formula (I) or a protected form thereof and thereafter, as necessary, carrying out one or more of the following steps:

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- (i) converting one compound of formula (I) into another compound of formula (I);
- (ii) removing any protecting group;
- (iii) preparing a salt or a solvate of the compound so formed.

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16. A pharmaceutical composition comprising a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

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17. A method for the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals which method comprises the administration of an effective non-toxic amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof.

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18. A method for the treatment of osteoporosis and related osteopenic diseases in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.
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19. A method for the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia, viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by Helicobacter pylori), autoimmune diseases and transplantation, for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours, in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.
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20. A compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.
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21. A compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals.
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22. A compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of osteoporosis and related osteopenic diseases.
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23. A compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for use in the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia, viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by
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Helicobacter pylori), autoimmune diseases and transplantation, for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours, in a human or non-human mammal

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24. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of diseases associated with over activity of osteoclasts in mammals.

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25. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of osteoporosis and related osteopenic diseases.

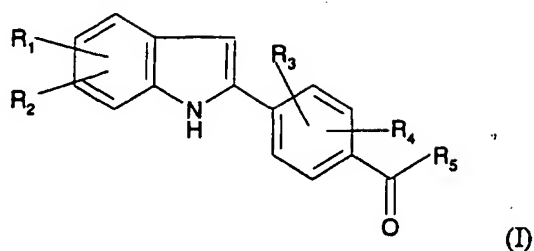
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26. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment of tumours, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia., viral conditions (for example those involving Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A and B, HIV viruses), ulcers (for example chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), autoimmune diseases and transplantation, for the treatment and/or prevention of hypercholesterolemic and atherosclerotic diseases, AIDS and Alzheimer's disease, angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours.

25

Abstract

A compound of formula (I)



or a salt thereof, or a solvate thereof, a process for the preparation of such a compound, a pharmaceutical composition containing such a compound and the use of the compound or composition in medicine wherein;

- 10 R₁ and R₂ each independently represents methoxy or chloro;
 R₃ and R₄ each independently represents hydrogen or alkoxy, and;
 R₅ represents -NR_sR_t wherein R_s and R_t each independently represent hydrogen, unsubstituted or substituted alkyl, or unsubstituted or substituted heterocyclyl.

